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Lessons learned from COVID-19 in relation to IVD regulations

CONTENTS

The Birmingham Health Partners Centre for Regulatory Science & Innovation was established in 2020 to support the development and delivery of novel therapeutics and medical devices in the UK, through advanced regulatory standards and tools. A truly multidisciplinary initiative, the CRSI aims to bring together experts in medicinal science, health policy and management, clinical trial design, medical law, and patient-reported outcomes research, from across BHP member organisations. The mission of the CRSI is to drive innovation in regulatory science to promote efficient, safe, and cost-effective implementation of new therapies, for the benefit of patients and society. **www.birminghamhealthpartners.co.uk**

The Regulatory Horizons Council (RHC) is an independent expert committee that identifies the implications of technological innovation, and provides government with impartial, expert advice on the regulatory reform required to support its rapid and safe introduction.

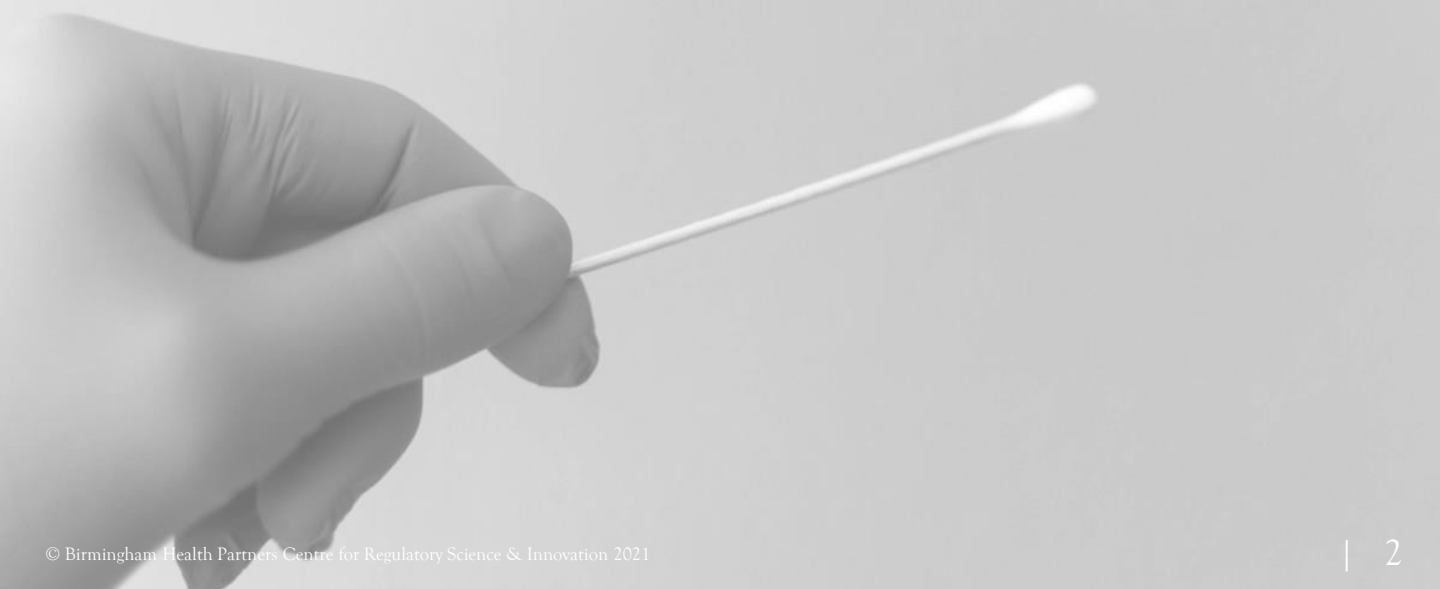
March 2021

Executive Summary

In vitro diagnostics (IVDs) are medical devices intended for use in diagnosis of disease or other conditions. The COVID-19 pandemic has clearly highlighted the importance of diagnostic tests in infectious disease outbreaks. The Regulatory Horizons Council commissioned the Birmingham Health Partners Centre for Regulatory Science and Innovation (CRSI) to collate lessons learned from COVID-19 in relation to IVD regulations by identifying the 'key challenges that have arisen around the application of IVD regulations during the COVID-19 pandemic' and the 'strategies that could be adopted to overcome the key challenges in the event of a future infectious disease outbreak'.

The CRSI team began by performing a literature review using PubMed and Google Scholar to search the published literature and Google Search Engine to search the grey literature. We then used three qualitative methods to comprehensively collate the lessons learned by stakeholders from across the medical device sector: i) one-on-one, semi-structured interviews with stakeholders were conducted; ii) a multidisciplinary stakeholder workshop was convened to review initial findings and discuss areas of agreement and disagreement; and iii) a post-workshop survey was distributed to attendees to further explore areas of contention discussed during the workshop. All data were subsequently analysed using a framework approach.

The evidence gathering and stakeholder engagement process identified that, in the event of an infectious disease outbreak, high-quality diagnostic tests need to be robustly and rapidly developed, distributed, and disseminated. For that reason, we have categorised the key challenges that have arisen around the application of IVD regulations during the COVID-19 pandemic and the strategies that could be adopted to overcome them in the event of a future infectious disease outbreak into three categories: those most relevant to the quality of diagnostic tests; those most relevant to the development and distribution of diagnostic tests; and those most relevant to the dissemination of information relating to diagnostic tests.



Quality of diagnostic tests High-quality tests are crucial in containing and controlling an infectious disease outbreak. This is because the implications of inaccurate test results, in the case of false negatives, undermine containment efforts. Unfortunately, throughout the COVID-19 pandemic, many substandard tests have been made available on the market without high quality evidence as a result of inadequate IVD regulations. This is because test developers in the EU (under the In Vitro Diagnostic Directive (IVDD)) and in the US (under Emergency Use Authorization (EUA)) are able to self-certify their tests without regulatory verification. Stakeholders succinctly summarised that no test is better than a bad test; and suggested that, in the event of a future infectious disease outbreak, all claims made by test developers should be checked by regulators, and the requirements for test characteristic requirements should be reviewed with the contextual implications of inaccurate test results in mind. Stakeholders also suggested that greater emphasis should be placed on intended use and usability testing to ensure adequate test performance in the 'real world'.

Development and distribution of diagnostic tests The timely development and distribution of high-quality tests is essential in curtailing transmission. This is because, until the advent of a vaccine, testing is the most effective tool available to keep transmission under control. During the COVID-19 pandemic, the development and distribution of high-quality tests has been delayed for a number of reasons, including a lack of access to crucial SARS-CoV-2 reference materials; a lack of clear and comprehensive COVID-19 specific guidance for test developers; regulators not being able to meet the surge in demand for their IVD and non-IVD-related services; and regulators not being able to carry out important in-person physical audits due to social restrictions. Stakeholders made multiple suggestions for how to increase efficiency in test development and distribution in the event of a future infectious disease outbreak: ensure access to pathogen-specific reference materials; provide clear and comprehensive situation-specific guidance for test developers; train and retain IVD regulatory experts; plan for and permit remote auditing; establish a permanent diagnostic unit with in-house clinical and regulatory expertise; use target product profiles (TPPs); develop common specifications; make routine health data more readily available; digitise the regulatory approval process; ensure continued access to laboratory-developed tests (LDTs); and increase the emphasis placed on post-market surveillance.

Dissemination of information relating to diagnostic tests The effective dissemination of test-related information is critical in combating an infectious disease outbreak. Enormous amounts of information have been disseminated from disparate sources during the COVID-19 pandemic and the quality of the information has been hugely variable. This has created confusion amongst patients and the public and made consumers more vulnerable to scams from unscrupulous suppliers. Data sharing practice amongst scientists has also been inadequate. Strategies to improve the dissemination of information in the event of a future infectious disease outbreak include developing best practice guidance for communicating complex information to patients and the public; investing in communication campaigns; and ensuring that information is presented in standardised formats, both online and in the scientific literature.

Key Findings

Challenges that have arisen around the application of IVD regulations during the COVID-19 pandemic

Quality

Self-certification meant that many COVID-19 tests were made available on the market without regulatory verification.
The unprecedented demand for COVID-19 tests has meant that regulatory authorities have had to adapt their policies and practices to ensure that tests could be made available on the market without delay. In the EU, under IVDD, and in the US, under EUA, developers have been able to self-certify their tests without regulatory verification, which has resulted in significant numbers of substandard tests being made available on the market.

Test characteristic requirements were not reviewed with the implications of inaccurate COVID-19 test results in mind. The requirements for test characteristics such as sensitivity, specificity, positive predictive value, and negative predictive value, were not reviewed with the implications of inaccurate COVID-19 test results in mind. This meant that many poor-quality tests with high false positive rates (which increase the likelihood of an uninfected individual self-isolating and worrying unnecessarily) and false negative rates (which increase the likelihood of disease being spread unknowingly by infected individuals with undetected infection) were made available on the market.

Insufficient emphasis was placed on the intended use of different COVID-19 tests.
The implications of a test's outcomes, and, by extension, the performance requirements for that test, differ depending on the situation in which the test is used. For example, the implications of and performance requirements for a test designed to screen healthcare professionals for immunity are different to those designed to diagnose patients with active infection. During the COVID-19 pandemic, insufficient emphasis was placed on the intended use of different tests, which raised the risk of tests being used inappropriately.

Development and distribution

Regulators have struggled to meet the surge in demand for their services due to the significant numbers of novel diagnostic tests that have been developed during the COVID-19 pandemic.
Significant numbers of novel diagnostic tests, non-IVD devices, new drugs, and vaccines have been developed during the COVID-19 pandemic and regulators have struggled to meet the surge in demand for their services. The increased burden placed on regulators has been exacerbated by unique COVID-19 related challenges, such as the reorganisation of clinical services, which has meant that fewer clinicians are available to advise regulators, and social restrictions, which have prevented essential in-person physical audits from taking place.

Lack of clear and comprehensive COVID-19-specific guidance for IVD developers.
A lack of clear and comprehensive COVID-19 specific guidance from regulators made it difficult for IVD developers to navigate the regulatory approval process during the pandemic.

Variable access to crucial SARS-CoV-2 reference materials. Pathogen-specific reference materials are essential when developing and validating tests. During the COVID-19 pandemic, there have been issues around access to crucial SARS-CoV-2 reference materials, which have impeded test development and validation.

Dissemination of information

Lack of accessible, clear, timely, and understandable information about COVID-19 tests for patients and the public.
Enormous amounts of information about tests have been disseminated from disparate sources during the COVID-19 pandemic and the quality of this information has been hugely variable. This has made it difficult for patients and the public to compare different test types, interpret test characteristics, and, ultimately, understand what is best for them. Unscrupulous suppliers have sought to capitalise on the confusion and the increase in demand for home testing kits by selling unsafe and unlicensed tests online, sometimes seeking to scam consumers via fraudulent websites.

Insufficient emphasis was placed on the importance of using reporting guidelines for studies involving COVID-19 tests.
Reporting guidelines specify the minimum content needed when reporting a study. Their use helps to improve the design, delivery, and evaluation of studies. During the COVID-19 pandemic, insufficient emphasis was placed on the use of reporting guidelines for studies involving IVDs. This made it difficult for developers to design and deliver high-quality studies and for reviewers to effectively evaluate them.

Widespread use of preprint servers for sharing COVID-19 test-related data before peer review. Peer review describes the process of subjecting scientific research to the scrutiny of others who are experts in the same field. It functions to ensure that unwarranted claims and interpretations are not published inappropriately. During the COVID-19 pandemic, preprint servers have been widely used to disseminate IVD-related data whilst awaiting peer review. The timely sharing of information is important during a pandemic but doing so prior to peer review increases the likelihood that poor quality, potentially misleading data are disseminated inappropriately.

Key Findings

Strategies that could be adopted to overcome the key challenges in the event of a future infectious disease outbreak

Quality

Regulatory oversight should be required for all tests. Although self-certification may be appropriate for low-risk tests most of the time, regulatory oversight should be required for all relevant diagnostic and screening tests in the event of a future infectious disease outbreak, to ensure that all claims made by IVD developers regarding test performance are reviewed.

Test characteristic requirements should be reviewed with the contextual implications of inaccurate test results in mind. In the event of a future infectious disease outbreak, the requirements for test characteristic requirements should be reviewed, with the contextual implications of inaccurate test results in mind, as these are likely to be different than they would be during normal times. Where possible, some aspects of test characteristic requirements can be prespecified based on lessons learned during the COVID-19 pandemic to increase readiness for a future infectious disease outbreak.

Greater emphasis should be placed on usability testing. The usability of a test is a key determinant of whether it will work when deployed at scale. For this reason, greater emphasis should be placed on usability testing in the event of a future infectious disease outbreak.

Development and distribution

Train and retain IVD regulatory experts. The ability for regulatory bodies to respond to surges in demand for their IVD-specific services during a future infectious disease outbreak could be improved by investing in training new, and retaining existing, IVD regulatory experts.

Plan for and permit remote auditing. It is possible that social restrictions that prevent in person physical audits from taking place will be re-instituted in the event of a future infectious disease outbreak. To prepare for such an eventuality, it is important for regulators to plan for and permit remote auditing.

Establish a national diagnostic unit with in-house clinical and regulatory expertise. Having a national diagnostic unit with in-house clinical and regulatory expertise in place that could be mobilised when needed would enable healthcare authorities to efficiently respond to a future infectious disease outbreak. In the UK, this could sit within the Department of Health and Social Care (DHSC).

Provide clear and comprehensive situation-specific guidance for IVD developers. In the event of a future infectious disease outbreak, clear and comprehensive situation-specific guidance would help IVD developers more easily overcome any challenges that they may face whilst navigating the regulatory approval process. Some guidance could potentially be prespecified.

Use target product profiles. A TPP outlines the desirable characteristics and minimally acceptable specifications of a product that is needed to address a well-defined clinical problem. In the event of a future infectious disease outbreak, TPPs should be used to drive the development of IVDs.

Develop common specifications. Common specifications are clinical and technical requirements – other than a standard – that provide a means of complying with legal obligations applicable to a device, process, or system. They are useful in situations where standards do not exist or are insufficient. Key stakeholders should consider developing common specifications to help guide IVD developers for use in the event of a future infectious disease outbreak when standards are unlikely to exist.

Make routine health data more readily available. Access to health data may be of a value when developing and validating a test. Making routine health data more readily available to IVD developers in the event of a future infectious disease outbreak would facilitate the development and validation process.

Digitise the regulatory approval process. Paper-based systems may be associated with delay and are less flexible when responding to a need to conduct audits and review virtually. Digitising the regulatory approval process would speed up the process and overcome potential challenges that may be posed during a future pandemic.

Ensure continued access to laboratory-developed tests. An LDT is a non-commercial IVD that is designed, manufactured, and used within a single laboratory. At the start of the COVID-19 pandemic, when no commercial tests were available on the market, it was LDTs that were initially used to diagnose patients with COVID-19. It is essential that future IVD regulation continues to ensure patient and public access to these tests, which will invariably play an important role in the event of a future infectious disease outbreak.

Ensure access to pathogen-specific reference materials. Efforts should be made to ensure effective distribution of pathogen-specific reference materials in the event of a future infectious disease as they are essential for the development and validation of tests. In the UK, the Medicines and Healthcare products Regulatory Agency and the National Institute for Biological Standards and Control would be well placed to organise and oversee this process.

Increase the emphasis placed on post-market surveillance. In the event of a future infectious disease outbreak, increasing the emphasis placed on post-market surveillance will ensure early access to essential tests, whilst enabling effective real-world evaluation of test performance.

Dissemination of information

Provide patients and the public with accessible, clear, timely, and understandable information. The COVID-19 pandemic demonstrated the importance of high-quality, test-related information and highlighted how hard communicating this kind of information to patients and the public can be. Authorities should invest in developing best practice guidance for communication about tests and ensure it is employed in the event of a future infectious disease outbreak. Online shops selling direct-to-consumer home testing kits should be made to present test-related information in a standardised manner.

Promote the use of standardised reporting guidelines for studies involving IVDs. The Standards for Reporting of Diagnostic Accuracy Studies (STARD) reporting guidelines specify the minimum content needed when reporting a diagnostic accuracy study. The use of STARD reporting guidelines should be promoted, as their use helps to improve the design, delivery, and evaluation of such studies.

Abbreviations

BHP	Birmingham Health Partners
CRSI	Centre for Regulatory Science and Innovation
COVID-19	Coronavirus disease
EU	European Union
EU IVDD	European Union In Vitro Diagnostic Directive (98/79/EC)
EUA	Emergency Use Authorization
IVD	In vitro diagnostic
LDT	Laboratory-developed test
RHC	Regulatory Horizons Council
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
STARD	Standards for Reporting of Diagnostic Accuracy Studies
TPP	Target product profile
UK	United Kingdom of Great Britain and Northern Ireland
US	United States

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This report reflects the views of a range of stakeholders and should not be attributed to specific individuals or organisations unless explicitly stated.

Drs Han and Ibrahim contributed equally to this report and are recognised as joint first authors.

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*Advisory board members

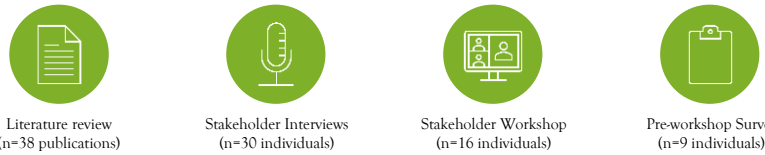
APPENDIX 1: Methods

Qualitative methods were used to collate the views of stakeholders from across the medical device sector.

1. Data Collection

Data were collected from four sources:

Figure 1. Data Sources.



1.1. Literature Review

A literature review was conducted on 08 January 2021. PubMed and Google Scholar were used to search published literature and Google Search Engine was used to search grey literature. Only the first 100 citations from Google Scholar and Google Search Engine were screened due to time constraints. Citations were independently screened by two co-investigators (DH and HI) according to predefined inclusion and exclusion criteria. Disagreements were resolved via consensus. A total of 38 citations were included in the literature review.

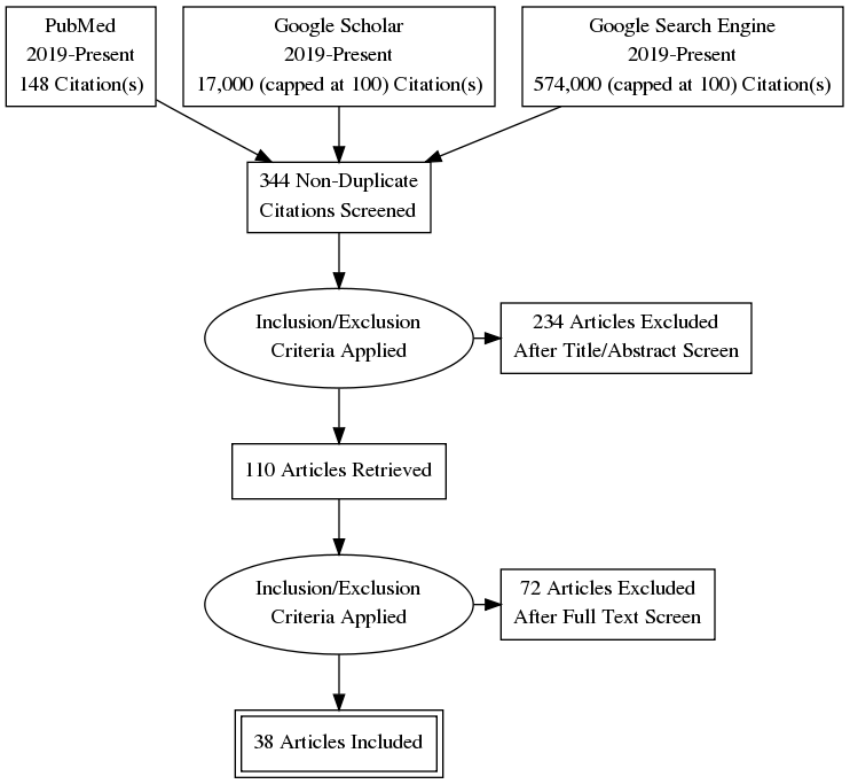
Table 1. Search Terms

PubMed		Google Scholar	Google Search Engine
Search Terms	Record no.	covid-19 "in vitro" medical devices regulation UK	covid-19 "in vitro" medical devices regulation UK
1 (in vitro diagnostic devices) or (in vitro diagnostic device) or (In vitro diagnostic medical device) or (In vitro diagnostic medical devices) or (IVDD) or (IVDDs) or (in vitro device) or (in vitro devices)	164,048		
2 (SARS-CoV-2) or (COVID-19) or (Coronavirus disease)	98,993		
3 ((in vitro diagnostic devices) or (in vitro diagnostic device) or (In vitro diagnostic medical device) or (In vitro diagnostic medical devices) or (IVDD) or (IVDDs) or (in vitro device) or (in vitro devices)) AND ((SARS-CoV-2) or (COVID-19) or (Coronavirus disease))	191		
4 (COVID-19 testing) or (COVID-19 related medical device) or (COVID-19 related medical devices)	8,050		
5 "In vitro"	1,548,996		
6 ((COVID-19 testing) or (COVID-19 related medical device) or (COVID-19 related medical devices)) AND ("In vitro")	106		
7 (((in vitro diagnostic devices) or (in vitro diagnostic device) or (In vitro diagnostic medical device) or (In vitro diagnostic medical devices) or (IVDD) or (IVDDs) or (in vitro device) or (in vitro devices)) AND ((SARS-CoV-2) or (COVID-19) or (Coronavirus disease))) OR (((COVID-19 testing) or (COVID-19 related medical device) or (COVID-19 related medical devices)) AND ("In vitro"))	283		
8 (Legislation) or (Legislations) or (Regulation) or (Regulations) or (regulatory) or (authorization) or (authorisation) or (approval)	5,238,406		
9 ((((in vitro diagnostic devices) or (in vitro diagnostic device) or (In vitro diagnostic medical device) or (In vitro diagnostic medical devices) or (IVDD) or (IVDDs) or (in vitro device) or (in vitro devices)) AND ((SARS-CoV-2) or (COVID-19) or (Coronavirus disease))) OR (((COVID-19 testing) or (COVID-19 related medical device) or (COVID-19 related medical devices)) AND ("In vitro"))) AND ((Legislation) or (Legislations) or (Regulation) or (Regulations) or (regulatory) or (authorization) or (authorisation) or (approval))	148		

Table 2. Inclusion and Exclusion Criteria for Literature Review.

Inclusion criteria	Exclusion criteria
English language	Non-English language
Published on or after 01 December 2019	Published on or before 30 November 2019
In vitro diagnostic medical devices	Does not clearly specify in vitro diagnostic medical devices in title or abstract
Regulation	Does not clearly specify regulation in title or abstract
Debates, discussions, lessons learned, opinions, reflections, and views about application of in vitro diagnostic medical devices regulation	Factual information about about application of in vitro diagnostic medical devices regulation

Figure 2. Flow Diagram for Literature Review.



1.2. Stakeholder Interviews

Stakeholder interviews were conducted online via MS Teams between 04 January 2021 and 02 February 2021. A total of 30 one-on-one, semi-structured interviews were conducted with stakeholders from across the medical device sector: medical device companies (n=7), regulatory consultancies (n=6), UK Government agencies (n=5), product testing or certifying bodies (n=4), academics and clinicians (n=4), trade associations (n=2), and patient and public partners (n=2).

1.3. Stakeholder Workshop

A workshop was conducted online via MS Teams on 09 February 2021. The aim of the workshop was to discuss areas of agreement and disagreement identified after analysis of data from the literature review and stakeholder interviews. A total of 16 stakeholders attended the workshop.

1.4. Post-Workshop Survey

A post-workshop survey was conducted online via Qualtrics Survey Software between 19 February 2021 and 05 March 2021. The survey was designed to further explore areas of contention discussed during the workshop. A total of 9 stakeholders completed the survey.

2. Data Analysis

Data were managed and analysed thematically using the framework approach. This method allows a comprehensive review of collected narratives, that is driven by stakeholders' original accounts and literature review. Raw data from the four sources were analysed by two co-investigators (DH and HI). The interviews were reviewed and coded independently using the stakeholder interview questions as an initial thematic framework. Textual codes were grouped into clusters around similar and interrelated concepts and a matrix of themes were created and analysed within Google Sheets.

3.1. Literature Review

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